Journal of Surgical Oncology 1997;66:277–281

HOW I DO IT

Lymphatic Mapping and Sentinel Node Harvest for Malignant Melanoma

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INTRODUCTION

The care of patients with melanoma has changed in the last 5 years with the development of new lymphatic mapping techniques to reduce the cost and morbidity of nodal staging, the emergence of more sensitive assays for occult melanoma metastases, and the identification of interferon alfa-2b as an effective adjuvant therapy for the treatment of patients with melanoma at high risk for recurrence. The accurate staging of melanoma patients has become more important in light of the recent report of a multicenter, prospective, randomized trial that shows a survival benefit for patients with T4 (tumor thickness > 4.0 mm) or Stage 3 (nodal metastases) melanoma who are treated with adjuvant interferon alfa-2b [1]. The lymphatic mapping technology is the least morbid and costly method to obtain nodal status of the patient with melanoma. Surgical technique is important, but it must be emphasized that the surgeon needs excellent nuclear medicine and pathology support to perform this technique.

THE ROLE OF NUCLEAR MEDICINE

Lymphoscintigraphy has been shown to be indispensable in predicting lymphatic basins at risk for the development of metastatic disease in patients with cutaneous malignant melanoma [2]. To further establish the efficacy of this method, 212 patients presenting to the H. Lee Moffitt Cancer Center (MCC) at the University of South Florida with primary melanoma of the head, neck, and trunk have been studied. All patients had clinical Stage 1 or 2 melanoma (clinically negative nodes) and were candidates for elective lymph node dissection (ELND). Drainage patterns identified by lymphoscintigraphy were compared to those predicted by historical anatomical guidelines and were found to be discordant in 63% of patients with tumors of the head and neck, and in 32% of those with primary lesions located on the trunk. Operative intervention was changed because of these findings in 47% of all patients, with 19% undergoing dissection of nonclassical lymph node basins. An additional 28% did not have a node dissection because of failure of the scintigram to demonstrate a predominant drainage basin or the demonstration of multiple drainage sites. This series has recently been updated to include over 600 mappings with a mean follow-up of 5 years. This is a period of time in which 85% of all the recurrences of melanoma should occur, yet there have been no recurrences in any basins not predicted at risk by lymphoscintigraphy. This simple test provides an extremely accurate depiction of all basins at risk for metastatic disease. The lymphatic drainage from cutaneous melanoma of the head, neck, and trunk cannot be reliably predicted by clinical judgement or classic anatomic guidelines and lymphoscintigraphy is indicated in these patients prior to ELND or SLN biopsy [2].

The preoperative lymphoscintigraphy serves as a road map for the surgeon and is used at MCC for four distinct reasons in planning the surgical procedure. These include:

1. To identify all nodal basins at risk for metastatic disease (Fig. 1).
2. To identify any intransit nodes that can be tattooed by the nuclear medicine physician for later harvesting. Intransit nodes occur in 5% of the melanoma population and may, by definition, be considered the SLN (Fig. 2).
3. To identify the location of the SLN in relation to the rest of the nodes in the basin [3]. The location of the SLN may be variable in a basin and ideally the surgeon needs a mark of the position of the SLN in reference to other nodes in the basin, in order to perform the harvest under local anesthesia with a minimal incision. Preoperative lymphoscitigrams can do this quite well. Twenty-nine patients with clinically

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Accepted 28 August 1997

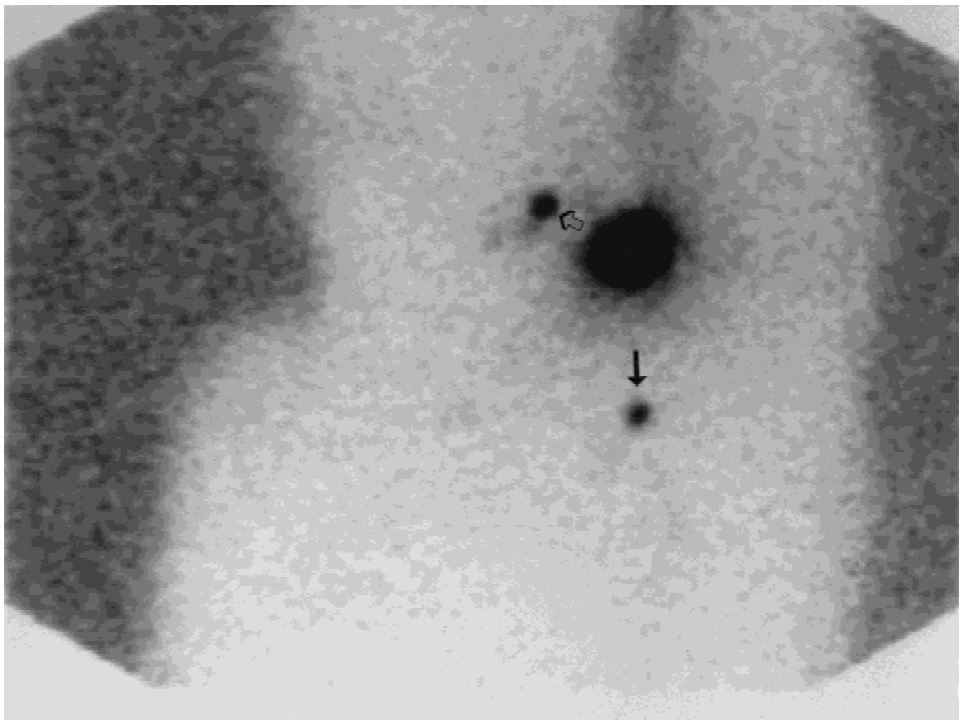

Fig. 1. 50-year-old white male with an ''intermediate thickness'' melanoma on the left shoulder. The body outline for anatomical orientation is created with a cobalt fluid source placed behind the patient. Preoperative lymphoscintigraphy with Technetium Sulfur Colloid shows bidirectional drainage to sentinel nodes in both the left neck (open arrow) and left axilla (closed arrow). Both basins are at risk for metastatic disease, while the clinical prediction would be for drainage to just the left neck. Intraoperative lymphatic mapping harvested the SLN in both locations with the neck being negative and the axilla having micrometastatic disease.

negative nodes and melanomas greater than 0.76 mm had preoperative lymphoscintigrams in two planes to mark the location of the SLN prior to operation. Thirty-three percent of the time the clinician could not predict the approximate location of the SLN within 5 cm, but the lymphoscintigraphy was accurate in the identification of the location of the SLN within 1.0 cm 100% of the time [3]. The technique was most accurate in the groin and the head and neck where the lymph nodes are more superficial. The axilla is the most difficult area to map and the best the preoperative lymphoscintigram can do in this basin is to tell the surgeon whether the node is located anterior, posterior, superior or inferior in the basin.

4. To estimate the number of SLN in the regional basin that will need to be harvested.

Some groups do not routinely perform pre-operative lymphoscintigraphy for lymphatic mapping, preferring to ''scan the body'' with a hand-held gamma probe at the time of the operation. This seems incredibly inefficient and time consuming. Metastatic disease may be missed and patients will be inaccurately staged.

DESCRIPTION OF THE TECHNIQUE OF INTRAOPERATIVE LYMPHATIC MAPPING

There is great variation from center to center on the technique of intraoperative mapping. This section will discuss the nuances of the technique, detailing the steps that are important to achieve successful mapping.

The timing of the injection of the mapping reagents is critical to the success of the procedure. Some compounds like the vital blue dye travel to the regional basin and through the first node in minutes, while some radiocolloids are concentrated over hours in the SLN. Localization ratios for ^{99m}Technetium-Sulfur Colloid (TC-SC) are greatest 2–4 hours after injection [4], accomplishing three points that are helpful for the surgeon. The increased ratios (hot spot/background, SLN/neighboring non-SLN) allow for easier localization. The prolonged retention in the SLN(s) permits the radiocolloid to be injected by a nuclear radiologist hours prior to the actual operation. Accordingly, the actual injection can be performed in the nuclear medicine area and surgeons do not need special licenses for radioactivity handling. Finally, scheduling of cases becomes more convenient, as there is a period of time (2–4 hours after injection of the radiocolloid) in which the intra-operative mapping easily can be accomplished.

Patients at MCC come to the nuclear medicine suite early the day of the surgery and undergo preoperative lymphoscintigraphy with the injection of 450 μCi of filtered ^{99m}TC-SC around the primary site. Dynamic scans are performed 5–10 min after the injection of the radiocolloid and the location of the SLN is marked in the basin

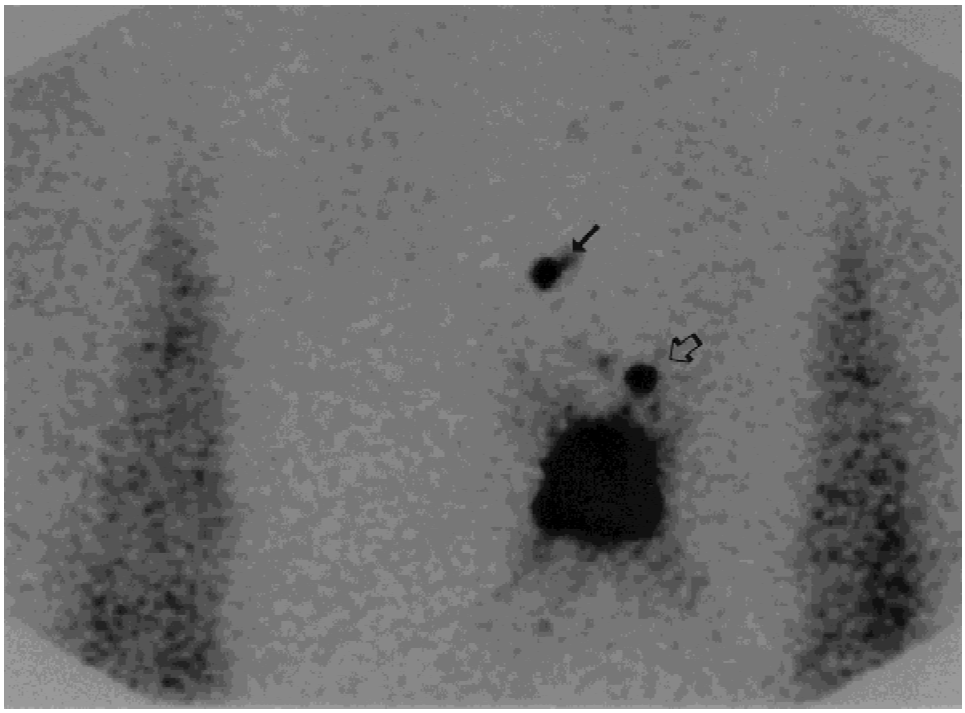

Fig. 2. 35-year-old white male with a 2.0 mm malignant melanoma excised from the left upper abdomen. Clinically the predicted cutaneous lymphatic flow would be to the left axilla. With preoperative lymphoscintigraphy, the left axilla is found not to be at risk for metastatic disease, but lymphatic flow was noted to an intransit node in the left upper abdomen within 5 cm of the primary site and to a lower internal mammary node (closed arrow). With the use of the Neoprobe for intraoperative mapping, both nodes (open arrow) were harvested. Pathology was negative.

with an intradermal tattoo. All lymphatic basins at risk for metastatic spread, intransit nodes, and the SLNs in the regional basin are identified and marked for harvesting. The patient is then taken to the OR 2–4 hours later and 1 cc of 1% lymphazurin is injected around the primary site. After prepping and draping the primary site and regional basin and allowing 10 min for the vital blue dye to travel to the SLN, attention is directed initially to the regional basin. With the hand-held gamma probe (Neoprobe Corporation, Dublin, OH), the ''hot'' spot in the regional basin is identified and the hot spot/background ratio is noted. If ''shine through'' from the primary site is a problem, the WLE of the primary may be performed first. An incision is made over the hot spot and small flaps are created in all directions to allow identification of the blue-stained afferent lymphatics. Surgical dissection is aided by both visualization of the stained afferent lymphatic down to the blue-stained node and by the use of the hand-held gamma probe. At times, the surgeon can be confused as to what is proximal or distal on the afferent lymphatic and the probe can be used to identify the direction of the dissection. The SLN is identified and removed with sharp or electrocautery dissection. The entire SLN is removed and afferent and efferent lymphatics from the SLN, some of which are identified with blue staining, are controlled with hemoclips, since the electrocautery does not seal lymphatics. This technique decreases the chance of postoperative wound seroma.

The excised SLN is checked with the gamma probe to ascertain whether it is radioactive in order to correctly identify it as the SLN. The radioactivity in the basin is checked with the gamma probe after removal of the SLN to assure that all SLNs have been removed. If radioactivity has not decreased to background, use of the hand-held gamma probe to direct additional dissection, will minimize the creation of unnecessary flaps when looking for additional blue-stained afferent lymphatics.

A secondary benefit of the radiocolloid mapping is immediate verification that all the SLNs have been removed from the basin. The level of radioactivity will return to background once the radiolabeled lymph nodes are removed. This avoids the additional dissection necessary to verify that all SLNs have been excised when only using the vital dye. In addition, in contrast to the blue dye, the colloid has a much longer retention time and may be concentrated in the SLN. Studies from MCC [4] and Henry Ford Hospital [5] have shown that the localization ratios double if the harvest occurs 2–4 hours after the injection of the radiocolloid compared to performing the mapping immediately after the injection of the radiocolloid.

The use of the radiocolloid for intraoperative mapping allows for excision of the SLN in unusual locations, such as the intransit nodes. Figure 2 illustrates the preoperative lymphoscintigraphy of a patient with an ''intermediate thickness'' melanoma of the left abdominal wall.

An intransit node (open arrow) is noted within 5 cm of the primary site with further drainage noted to a node in the lower left internal mammary chain (closed arrow). Of note is that there is no axillary or superficial groin drainage, as would have been clinically predicted.

The radiocolloid and vital blue dye mapping techniques are complimentary and there is no reason why both should not be used simultaneously to increase the success rate of localization of the SLN. The different mapping techniques are important depending on the location of the primary in relation to the regional basin. If the primary site is close, overlying or in a direct line to the basin so that the hand-held gamma probe will detect ''shine through'' from the residual radioactivity at the primary site, use of the vital blue dye may be the only technique that allows for a successful mapping. Only 1% of the injected dose of the radioactivity is delivered to the regional basin, so even if the radioactivity from the primary is lowered by performing the WLE first, enough radioactivity may be present from the primary site injection to increase the background in the basin to a level that mapping with only the radiocolloid mapping is impossible. In contrast, in patients with a fatty axilla or in head and neck mapping, it may be impossible to follow a wisp of a blue-stained afferent lymphatic to the SLN. Particularly in the head and neck area, because of the presence of surrounding vital structures, large flaps are to be avoided and the ability of the gamma probe to locate the ''hot'' spot through the skin is a tremendous advantage.

SLNs are defined as those nodes either in an intransit location or in the regional basin that receives lymphatic flow from the primary melanoma. They can be identified by following a blue-stained afferent lymphatic to a blue-stained node, as originally described by Morton [6] or with the Neoprobe and a localization ratio (SLN/neighboring non-SLN) of 10/1 [4]. Using this technique and these definitions of the SLN, the success rate of harvesting this first node at MCC is 96% [4].

ROLE OF PATHOLOGY

After harvesting, the SLN is submitted for a detailed histologic examination that may include serial sectioning, immunohistochemical staining with S-100 and HMB-45 monoclonal antibodies and perhaps newer assays using molecular biology techniques for occult metastases [7]. Historically, the routine pathological exam of regional nodes includes making 1–2 sections of the central cross-section of the node and submitting for routine stains. This standard of care examined less than 1% of the submitted material and yet pathological diagnoses were reported, prognoses were determined, and treatment decisions were made based on a pathologist examining less than 1% of the material. Invariable micrometastatic disease was missed and patients were inadequately staged. An added advantage of the lymphatic mapping technology is that now a surgeon can give a pathologist 1–2 nodes in order to perform a more detailed examination. This will increase the sensitivity of the examination and provide for a more accurate staging.

Previous studies have demonstrated the efficacy of SLN mapping with a false negative rate, defined as a negative SLN with positive higher nodes, to be less than 4%, as determined by concomitant formal lymph node dissection [8,9]. However, the long term risk of failure within the mapped nodal basin after a negative SLN alone was unclear. This issue was addressed by a recent study from M.D. Anderson Cancer Center and MCC [10]. Patients diagnosed with cutaneous melanoma and a tumor thickness of at least 1.0 mm and/or Clark Level IV were eligible for mapping and SLN biopsy. All patients underwent pre-operative lymphoscintigraphy and only patients with a histologically positive SLN biopsy underwent subsequent complete lymph node dissection. Patients with a histologically negative SLN did not undergo complete lymphadenectomy. Intraoperative mapping consisted of either a vital blue dye injection alone or in combination with Tc-99-labeled sulfur colloid. Six-hundred eighteen patients underwent mapping with successful identification of at least 1 SLN. Of these 518 were pathologically negative by routine histology. After a minimum follow-up of 3 months and a median follow-up of 18 months, 32 of the 518 patients (6%) developed recurrent disease. Nine of 518 patients (1.7%) developed their first recurrence in a previously mapped negative SLN basin. Patients with a histologically negative SLN had a significantly improved disease free survival ($P < 0.001$) and distant disease free survival ($P < 0.001$) compared to those with a histologically positive SLN biopsy. Lymphatic mapping and SLN biopsy was an effective staging procedure, and just as accurate as ELND. Retrospective re-examination of SLNs in nine patients whose SLNs were determined to be free of metastatic disease on initial review by routine histology revealed occult nodal metastases in seven patients (77%), by either serial sectioning, immunohistochemistry, or polymerase chain reaction (PCR) analysis for tyrosinase. These data established the durable long term accuracy of lymphatic mapping and SLN biopsy. Optimal nodal staging requires both an accurate identification and biopsy of the SLN and careful examination of the SLN using special pathology techniques. False negative SLN biopsies may be a result of missed micrometastases on routine pathological examination rather than true ''skip'' metastases.

REFERENCES

1. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum R: Interferon alfa-2b adjuvant therapy of high-risk re-

sected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7–17.
2. Norman J, Cruse CW, Espinosa C, et al.: Redefinition of cutaneous lymphatic drainage with the use of lymphoscintigraphy for malignant melanoma. Am J Surg 1991;162:432–437.
3. Godellas CV, Berman C, Lyman G, et al.: The identification and mapping of melanoma regional nodal metastases: Minimally invasive surgery for the diagnosis of nodal metastases. Am Surg 1995;61:97–101.
4. Albertini JJ, Cruse CW, Rapaport D, et al.: Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. Ann Surg 1996;223:217–224.
5. Nathanson SD, Anaya P, Eck L: Sentinel lymph node uptake of two different radionuclides [abstract]. In The Society of Surgical Oncology 49th Cancer Symposium meeting program; 1996 March; Atlanta, GA.
6. Morton DL, Wen DR, Cochran AJ: Management of early-stage melanoma by intraoperative lymphatic mapping and selective lymphadenectomy or ''watch and wait.'' Surgical Oncology Clinics of North America 1992;1:247–259.
7. Wang X, Heller R, VanVoorhis N, et al.: Detection of submicroscopic metastases with polymerase chain reaction in patients with malignant melanoma. Ann Surg 1994;220:768–774.
8. Reintgen DS, Cruse CW, Berman C, Ross M, Rapaport D, Glass F, Fenske N, Messina J: An orderly progression of melanoma nodal metastases. Ann Surg 1994;220:759–767.
9. Ross M, Reintgen DS, Balch C: Selective lymphadenectomy: Emerging role of lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. Sem Surg Oncol 1993; 9:219–223.
10. Gershenwald J, Thompson W, Mansfield P, Lee J, Colome M, Balch C, Reintgen D, Ross M: Patterns of failure in melanoma patients after successful lymphatic mapping and negative sentinel node biopsy [abstract]. In The Society of Surgical Oncology 49th Cancer Symposium meeting program; 1996 March; Atlanta, GA.